ROCK Inhibition Promotes Attachment, Proliferation, and Wound Closure in Human Embryonic Stem Cell-Derived Retinal Pigmented Epithelium.

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Public Summary:
Nonexudative (dry) age-related macular degeneration (AMD), a leading cause of blindness in the elderly, is associated with the loss of retinal pigmented epithelium (RPE) cells and the development of geographic atrophy, which are areas devoid of RPE cells and photoreceptors. One possible treatment option would be to stimulate RPE attachment and proliferation to replace dying/dysfunctional RPE and bring about wound repair. Clinical trials are underway testing injections of RPE cells derived from pluripotent stem cells to determine their safety and efficacy in treating AMD. However, the factors regulating RPE responses to AMD-associated lesions are not well understood. Here, we use cell culture to investigate the role of RhoA coiled coil kinases (ROCKs) in human embryonic stem cell-derived RPE (hESC-RPE) attachment, proliferation, and wound closure. METHODS: H9 hESC were spontaneously differentiated into RPE cells. hESC-RPE cells were treated with a pan ROCK1/2 or a ROCK2 only inhibitor; attachment, and proliferation and cell size within an in vitro scratch assay were examined. RESULTS: Pharmacological inhibition of ROCKs promoted hESC-RPE attachment and proliferation, and increased the rate of closure of in vitro wounds. ROCK inhibition decreased phosphorylation of cofilin and myosin light chain, suggesting that regulation of the cytoskeleton underlies the mechanism of action of ROCK inhibition. CONCLUSIONS: ROCK inhibition promotes attachment, proliferation, and wound closure in H9 hESC-RPE cells. ROCK isoforms may have different roles in wound healing. TRANSLATIONAL RELEVANCE: Modulation of the ROCK-cytoskeletal axis has potential in stimulating wound repair in transplanted RPE cells and attachment in cellular therapies. KEYWORDS: ROCK inhibition; age related macular degeneration; retinal pigment epithelium

Scientific Abstract:
PURPOSE: Nonexudative (dry) age-related macular degeneration (AMD), a leading cause of blindness in the elderly, is associated with the loss of retinal pigmented epithelium (RPE) cells and the development of geographic atrophy, which are areas devoid of RPE cells and photoreceptors. One possible treatment option would be to stimulate RPE attachment and proliferation to replace dying/dysfunctional RPE and bring about wound repair. Clinical trials are underway testing injections of RPE cells derived from pluripotent stem cells to determine their safety and efficacy in treating AMD. However, the factors regulating RPE responses to AMD-associated lesions are not well understood. Here, we use cell culture to investigate the role of RhoA coiled coil kinases (ROCKs) in human embryonic stem cell-derived RPE (hESC-RPE) attachment, proliferation, and wound closure. METHODS: H9 hESC were spontaneously differentiated into RPE cells. hESC-RPE cells were treated with a pan ROCK1/2 or a ROCK2 only inhibitor; attachment, and proliferation and cell size within an in vitro scratch assay were examined. RESULTS: Pharmacological inhibition of ROCKs promoted hESC-RPE attachment and proliferation, and increased the rate of closure of in vitro wounds. ROCK inhibition decreased phosphorylation of cofilin and myosin light chain, suggesting that regulation of the cytoskeleton underlies the mechanism of action of ROCK inhibition. CONCLUSIONS: ROCK inhibition promotes attachment, proliferation, and wound closure in H9 hESC-RPE cells. ROCK isoforms may have different roles in wound healing. TRANSLATIONAL RELEVANCE: Modulation of the ROCK-cytoskeletal axis has potential in stimulating wound repair in transplanted RPE cells and attachment in cellular therapies.

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